Mapping the global distribution of Buruli ulcer through a systematic review with an evidence consensus approach

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Mapping the global distribution of Buruli ulcer through a systematic review with an evidence consensus approach

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Summary

Background

Buruli ulcer can cause disfigurement and long-term loss-of-function. It is under-diagnosed and under-reported, and its current distribution is unclear. We aimed to synthesise and evaluate data on BU prevalence and distribution.

Methods

We conducted a systematic review of BU prevalence, and used an evidence consensus framework to describe and evaluate evidence for BU distribution worldwide. We searched online databases from inception to 06/08/2018 for records of BU and *M. ulcerans* detection, with no limits on study type, date, or location. We included population-based surveys presenting BU prevalence estimates in the systematic review, extracting prevalence estimates with 95% CIs. We extracted geographical data on the occurrence of BU cases and *M. ulcerans* detection from studies of any type. Occurrence records, reports to WHO and the Global Infectious Diseases and Epidemiology Network, and national BU surveillance data were included in an evidence consensus framework to grade the strength of evidence for BU endemicity. This study is registered with PROSPERO, number CRD42018116260.

Findings

2,763 titles met the search criteria. We extracted prevalence estimates from ten studies and occurrence data from 208. Prevalence estimates within study areas ranged from 3.2- 26.9 per 10,000. There was evidence of BU in 32 countries and consensus on presence in 12.

Interpretation

The global distribution of BU is uncertain, and potentially wider than currently recognised. These maps represent the strongest available evidence on BU distribution to date, and have many potential applications, from directing surveillance activities to informing burden estimates.

Funding

The AIM Initiative was the sole funder.

Background (343 words)

Buruli ulcer (BU) is a neglected tropical disease caused by the environmental pathogen *Mycobacterium ulcerans*. It primarily occurs in West and Central Africa, but also in parts of Asia, South America, the Western Pacific and Australasia.[1,2] It is considered an important public health problem due to the characteristic necrotic ulcers it causes, and the scarring and deformity which can persist after treatment.[3] Although its mode of transmission is not fully understood, contact with slow-flowing, stagnant, or disturbed water bodies is an important risk factor.[4]

BU was reported in 34 countries from 1960-2015,[4] but there is lack of consensus on where transmission currently occurs. Ten countries reported a total of 1,864 cases to the WHO in 2016,[1] but this is recognised to reflect a small proportion of the total burden. Cross-sectional surveys within endemic countries have demonstrated under-reporting of BU,[5-7] for reasons including the chronic, stigmatising nature of the disease, its rural distribution, patients' lack of access to healthcare or preference for traditional healers, and lack of awareness or resources within health systems.[4,8] Misdiagnosis may also contribute to under-detection: BU has a range of non-specific presentations which can be confused with other skin conditions, especially in the absence of confirmatory tests.[9,10] Therefore, available data does not provide a full or accurate representation of BU burden and distribution: essential information for targeting of active case detection, which is a key part of control,[3] and for directing resources for case management.

Estimating the global burden and population at risk of BU requires detailed information on the geographical limits and prevalence of the disease. We aimed to synthesise available data on BU prevalence and occurrence and environmental occurrence of *M. ulcerans*, including WHO reports, national surveillance programmes, the grey literature, and peer-reviewed literature. We undertook a systematic review of population-based studies reporting the prevalence of BU, providing a descriptive analysis of BU epidemiology within known-endemic areas. We used an evidence consensus approach[11,12] to delineate the overall distribution of previously reported cases and to quantify the strength of evidence for BU presence or absence in every country worldwide.

Methods (1266 words)

This review is registered in the PROSPERO International Prospective Register of systematic reviews; CRD42018116260.

Information sources

Data sources included peer-reviewed literature, conference proceedings and abstracts and government reports (grey literature), data reported to WHO from 2006-2017,[1] data reported through the GIDEON network,[13] and surveillance datasets from national BU programmes in Cameroon, Ghana, Nigeria and Togo. Peer-reviewed literature was identified from searches of PubMed and Web of Science databases, updated on 06/08/2018. Additional publications were identified from reference lists of identified papers.

Literature Search

We used the search terms (OR): "Buruli ulcer*", ("Mycob* AND ulcer*"), "Bairnsdale ulcer". There were no limits on publication date, study type, or location. We included English, French, and Spanish language publications. Details in section S.1.1, Supplementary File.

Eligibility criteria

Population-based BU surveys were included in the systematic review if they reported the prevalence of BU within a defined geographical area, or information allowing this to be calculated.

Publications were eligible for inclusion in the evidence consensus if they reported geographical locations with evidence of *M. ulcerans* infection in humans or animals, or detection of *M. ulcerans* in animal and environmental samples.

There were no limits on publication date, participant population, study type or location. Articles that did not report original data were excluded.

Study selection

Titles were screened to exclude non-relevant publications. Abstracts of selected records were screened to identify papers which apparently fulfilled selection criteria. Full texts of selected articles were read to identify studies meeting the selection criteria. Studies that recruited patients from health facilities or used strains of *M. ulcerans* isolated from clinical samples were included in the evidence consensus framework only if patients' home addresses were provided. Cases with recorded travel history to several endemic regions were excluded. If a dataset was duplicated in numerous papers, the most comprehensive was included.

Data extraction

Data from surveillance datasets and selected publications was extracted into a bespoke Microsoft Excel spreadsheet used for the Global Atlas of Helminth Infections.[14] The original spreadsheet was piloted on a subset of studies, and then developed. Authors were contacted for additional data if community-level results were not presented. The data extraction was performed by a single author and checked by a second one. Data extracted included: i) the number or prevalence of cases, ii) the sample size and survey coverage (for population-based studies) iii) the case detection method (survey, case search, passive detection), iv) the recording date, v) the diagnostic procedure, including any confirmatory tests (polymerase chain reaction (PCR) for *M. ulcerans* gene targets; Ziehl Neelsen (ZN) staining; culture for *M. ulcerans*; histopathological analysis) and their results, and vi) the location of origin (patient residence or endemic area visited if the case originated from a non-endemic area). Areas described as 'endemic', with no information on case detection, were not included.

Data extracted on environmental detection of *M. ulcerans* included: i) sample date and location, ii) sample type (water, soil, plant, animal- clinical, animal- faeces), iii) taxonomic details for animal samples, iv) confirmatory tests, and v) numbers of samples tested and positive.

Geographic coordinates of occurrence locations were extracted if were provided in the publication. Otherwise, point locations were georeferenced remotely (section S.1.2, Supplementary File). Point locations that could not be georeferenced were linked to the lowest administrative level provided in the publication. Polygon areas corresponding to first and second administrative divisions were linked to units defined in the Database of Global Administrative Areas.[15]

Summary measures

The principal summary measure for the systematic review was BU prevalence. The quality of prevalence studies was assessed using a framework based on the Newcastle-Ottawa score,[16] adapted from a systematic review of podoconiosis prevalence[17] (S.3. Supplementary File). This took account of the sampling frame, response rate, diagnostic specificity, and statistical analysis. The risk of outcome bias was assessed according to whether sampling was done at random or using convenience sampling within the study area. The number of studies from each country, relative to the number of cases reported to WHO, was used as an indicator of geographical bias between studies.

The outcome measures for the evidence consensus framework were BU and *M. ulcerans* occurrence. Occurrence locations were assigned local- and national-level quality scores reflecting contemporariness and specificity (S.1.3- S.1.4, Supplementary File). We used the number of studies included in the evidence consensus framework, and the number reporting laboratory confirmation, as indicators of geographical bias in reporting and study quality.

Data Synthesis

We extracted prevalence estimates from included surveys and calculated 95% confidence intervals (CIs) using Byar's method.[18]

Occurrence data was synthesised through an evidence consensus approach using a weighted scoring system, following that used to determine the global distribution of other diseases.[11,12] Separate frameworks were used to assess the evidence for BU presence or absence at national level (Figure 1), evidence for BU presence at sub-national level (Figure 2), and evidence for environmental occurrence of *M. ulcerans* at sub-national level (section S.1.5, Supplementary File).

National level

The major features for the national evidence framework were:

- *Health reporting organisations:* Countries were assigned a score based on recent and historical reporting to WHO and reports through GIDEON.
- *Occurrence data quality:* Each country was assigned the highest data quality score of occurrence records within it.
- *Number of cases:* The number of cases reported at each location was weighted by the local-level data quality score, and the weighted totals were aggregated to national level.
- *Evidence for absence:* In countries with no cases reported, the consensus score was designed to quantify the evidence for BU absence, reflecting the possibility of under-reporting due to (i) weak surveillance capacity, or (ii) misdiagnosis as known endemic diseases with similar presentations[19] (confounding diseases) (Figure 1B). As a proxy for surveillance and diagnostic capacity, health expenditure (HE) reported by WHO[20] was categorised as low (<$100), medium ($100≤HE<$500) or high (HE≥$500), following the approach of previous authors and supported by evidence that higher HE is associated with better health system performance[21].

  The confounding diseases with available evidence on their global distribution were: cutaneous leishmaniasis (CL),[12,22] leprosy,[23] lymphatic filariasis (LF),[14] onchocerciasis,[24] tropical ulcer (TU)[2] and yaws[25]. Estimates of the frequencies of the common presentations of these diseases and BU

were obtained from literature review and expert opinion.[24,26-29] For each confounding disease, the frequency of each presentation shared with BU was multiplied by the frequency of the presentation among BU cases, and the products summed to generate a symptom overlap score (Table S1, Supplementary File).

For each country, the symptom overlap scores for its endemic confounding diseases were summed, then down-weighted if HE was high or medium. This score was added to an ordinal HE score reflecting likelihood of under-detection/ non-reporting.

Figure 1 approximately here

Sub-national level

Each upper administrative level was assigned the highest local-level evidence quality score of the occurrence records which fell within it or within 5km distance of its boundaries, and a score reflecting total number of cases within the unit (Figure 2).

Figure 2 approximately here

Environmental occurrence of M. ulcerans

Environmental detection records were assigned to the upper administrative unit[15] they fell within. Each unit was assigned the highest evidence quality score of records within it, and a score reflecting the total number of detection records within it, weighted by evidence quality score (Table S2, Supplementary File).

Role of the funding source

The AIM Initiative was the sole funder of this work. The AIM Initiative facilitated connections with disease control programmes for data transfer, but had no input in the systematic review or decision to publish. Hope Simpson had full access to all data in the study and final responsibility for the decision to submit for publication.

Kebede Deribe is supported by the Wellcome Trust [grant number 201900] as part of his International Intermediate Fellowship. The Wellcome Trust has not played any role in the design, conduct, analysis, or writing up of the study.

Results (918 words)

Study selection

The literature search identified 2,849 records after de-duplication (Figure 3). Another 86 were identified through other sources. The most common reason for exclusion was lack of information on patient origin. Full text was unavailable for 46 studies. Ten BU prevalence surveys were included in the systematic review.[7,8,30-35] Occurrence data was extracted from 208 publications and five surveillance datasets.

Figure 3 approximately here

Study characteristics

Three surveys conducted in Cameroon, two in each of Benin, Cote d'Ivoire and Ghana, and one in the DRC (Table 1) were included. The largest was a national survey in Cote d'Ivoire, covering an estimated 14,500,000 people.[5]

Seven surveys provided explicit details on the sampling frame. All surveys were community-based and aimed to reach the entire population of chosen communities. Seven covered the entire study area, one surveyed randomly selected communities within the study area, one surveyed a convenience sample of communities and one used random and convenience sampling. Only one reported the survey coverage.[8] Five reported laboratory confirmation of all or a subset of cases, five used clinical case definitions. Only one study reported prevalence with 95% CIs.[8]

Overall prevalence estimates within the study area ranged from 3.2- 26.9 cases per 10,000. The highest reported community prevalence of BU was 2,200 per 10,000.[34]

Table 1 approximately here

Evidence consensus

Human cases were recorded from 32 countries, and inferred from two further countries from which strains were reported to have been isolated (Iran and Malaysia) [36,37]. Most cases (94·9%) were from the African (AFRO) region, 5·6% were from the West Pacific (WPRO) region, and less than 1% were from other WHO regions. Evidence of *M. ulcerans* in environmental and animal samples was reported from nine countries. A summary of data extracted from all publications is provided in Table S.3 of Supplementary File.

Cases were recorded from 1952- 2017, with the greatest number detected in 1999 (3,401). From 1952- 1998, between zero and five countries each year had evidence of BU based on peer-reviewed literature. The disease was identified in nine countries in 1999. Including data reported to WHO, available from 2002, between twelve and eighteen countries each year had evidence of BU.

Laboratory confirmation of at least one case was reported by 71% of studies included, and 62.5% used PCR. However, most occurrence records (77%) were categorised as clinically diagnosed only, because laboratory results were not disaggregated by unique locations.

Symptom overlap scores for the confounding diseases are shown in Table 2. TU had the highest score, reflecting the high frequency of ulcers among BU and TU.[2,35] BU was considered less likely to be misdiagnosed as CL or yaws, which present a lower frequency of ulcerous forms.[26,27] Onchocerciasis, leprosy and LF had symptom overlap scores below 6%.

Full results of the evidence consensus framework are provided at country level in Supplementary File, Table S.5.

Table 2 approximately here

We identified consensus on BU presence in twelve countries, which collectively reported 34,890 cases to WHO from 2002- 2016 (96·2% of all cases reported to WHO in this period). Australia and Japan were the only non-African countries with consensus on presence (Figure 4).

The African countries with evidence of BU were mostly clustered in a block covering much of Central and West Africa. Countries around this block generally had weaker evidence for absence, with a higher number of endemic confounding diseases and lower HE. In the AMRO region, evidence of BU was strong in French Guiana and Peru, and moderate in Brazil, Mexico and Suriname. Despite strong evidence of BU cases from French Guiana in literature reports, the disease has never been reported

to WHO, so full consensus on endemicity was not reached through the framework. There was moderate evidence for BU in China. Endemicity status was indeterminate in Burkina Faso, Ethiopia, Honduras, Indonesia, Malawi, Malaysia and Suriname. Niger, Eritrea, the Gambia, and Mauritania, all in the AFRO region, had the weakest evidence for absence, being endemic for CL and TU, and having low health expenditure. Fourteen other countries- of which 12 were in Africa- had weak evidence for absence.

Figure 4 approximately here

Sub-national areas with evidence for endemicity were mostly clustered within equatorial, humid tropical and tropical climate zones of West and Central Africa (Figure 5). Areas with evidence for BU in Eastern, Southern, and non-coastal Central Africa, and other parts of the world, were more isolated (Figures 5 and 6).

Figure 5 approximately here
Figure 6 approximately here

Buruli ulcer in animals and *M. ulcerans* in the environment

The areas with evidence of *M. ulcerans* in animal and environmental samples are shown in Figure 7. BU disease was reported in wild and domestic animals in Australia, Benin, Cameroon and Ghana, and *M. ulcerans* DNA has been detected in faecal samples from animals in Australia (details and references in Table S.4). DNA from mycolactone-producing environmental bacteria has been identified in biotic and abiotic samples from waterbodies in eight BU endemic countries, and the United States of America (details and references in Table S.4). However, it is not clear if the American strains would be capable of causing BU disease in humans.

Figure 7 approximately here

Discussion (1011 words)

We have collated available on BU prevalence and occurrence, and evidence of *M. ulcerans* in animals and the environment. The evidence consensus framework applied has allowed us to expand on existing maps of BU distribution [2,38] in several ways. The maps presented include evidence from a

wider range of sources, provide finer resolution, and quantify the strength of evidence for BU presence, as well as absence in countries where BU has not been reported.

There have been few BU prevalence surveys, and most of those identified did not report detailed statistical analysis or indicators such as coverage. *We did not undertake a meta-analysis because of the heterogeneous nature of compiled studies. Furthermore, most studies included were conducted in areas assumed to have a high rate of BU, so a summary prevalence would tend to overestimate the disease burden in the overall population.*

Prevalence estimates reported by population-based studies were high relative to incidence data reported through WHO. This is likely to reflect underreporting of BU through routine systems, but the studies included may have overestimated BU prevalence due to sampling bias. Two of the ten studies included[7,35] used convenience sampling as part of the study design, which implies a risk of bias in the estimated prevalence. Five studies reported clinical diagnosis according to WHO guidelines and five used laboratory confirmation to confirm all or a subset of cases. There was geographical bias across the studies included, representing only five countries out of the 32 identified as having evidence for BU.

Our investigation identified consensus on BU presence in eight of the ten countries accounting for 97% of BU cases reported to WHO from 2007- 2016. However, the maps presented demonstrate significant remaining uncertainty on the global distribution of BU. There was indeterminate or moderate quality evidence of BU in fifteen countries that had not reported data to WHO from 2007-2016.

The national and sub-national evidence consensus maps demonstrate large contiguous areas of potential endemicity, both within and between countries, particularly in Central and Western Africa. Evidence for BU presence was generally strongest in these contiguous areas. This is likely to be partly due to environmental similarity in terms of suitability, and partly due to increased emphasis on case detection in areas established as endemic.

The area of BU presence defined by the sub-national map of BU distribution in Africa (Figure 5) was more restricted than that defined by the map of national-level endemicity (Figure 4). This reflects the focal and restricted distribution of BU,[39] and the lower availability of data at subnational level: in some countries, the only available data was that reported to WHO, with no information on sub-national distribution. Given the recognised scale of BU under-reporting, it is likely that this map underestimates the scale of BU distribution.

Countries which had not reported BU cases, but were close to those that had, generally had weaker evidence for absence than countries located further from areas of BU endemicity. This trend was apparent in Africa, South America, and the South East Asia and Western Pacific regions, and reflects spatial clustering of countries with lower health expenditure and numerous co-endemic tropical diseases, irrespective of their evidence for BU. The proximity of BU-endemic countries to those with lowest evidence for BU absence adds further weight to the possibility that BU may occur undetected in the latter group, due to cross-border transmission and environmental similarity of neighbouring countries.

Limitations

While the maps provide finer detail on the distribution of BU than current official maps, they still mask the underlying epidemiology of BU. Areas identified as endemic may in fact contain only a few localised cases of BU, and be mostly unsuitable for the disease. Due to the focal nature of BU,[39] point-level data on disease occurrence is needed to support investigation into its spatial epidemiology. It is hoped that the maps and assembled geographic dataset will support such research in the future.

Studies on *M. ulcerans* environmental occurrence were limited, and many did not apply sufficiently specific tests to differentiate *M. ulcerans* from other environmental mycobacteria. Therefore, the maps of evidence for environmental occurrence of *M. ulcerans* do not provide a complete representation of environmental suitability for the bacterium. Although we assigned the maximum possible evidence quality score to clinical cases confirmed by PCR and environmental occurrences confirmed by q-PCR, these tests still entail a risk of false positives, as demonstrated by an external quality assessment including several reference laboratories which performed confirmatory testing in studies we included.[40]

There was marked geographical bias in the occurrence records, reflecting different levels of research and surveillance activity between countries. Further analysis of the data underlying this work should account for this bias. In the context of this study, this bias is expected to have impacted areas where there were few studies, but not where there were many studies, since additional studies would not change the outcome measure unless they provided higher quality data.

Implications

The areas with highest consensus for presence are presumably most suitable for BU transmission, and would be targets for surveillance and research since they represent known disease foci. Some countries with strong evidence for BU are not shown in the current WHO map of BU,[38] demonstrating that the disease is more widely distributed than the official map suggests. This has important implications for understanding and communicating the global burden of BU. We have also expanded upon the WHO map of BU by qualitatively grading the strength of evidence for endemicity. In doing so we have identified numerous countries with moderate or indeterminate evidence of BU, and those with weakest evidence for its absence, which may require further investigation to clarify the global distribution of BU. Active case finding in areas which have previously reported BU, and close to those currently reporting, should be prioritised. The assembled point-level dataset represents a novel resource for continent-wide exploration of environmental and biological predictors of BU, and estimation of the global burden and population at risk. The information provided by investigations such as these will help to target future control efforts and evaluate their impact.

Declaration of interests

None to declare

Data availability

All occurrence data extracted and georeferenced as part of this investigation will be made publicly available through the Dryad data repository upon publication of the manuscript.

Funding source

The AIM Initiative was the sole funder of this work. The AIM Initiative facilitated connections with disease control programmes for data transfer, but had no input in the systematic review or decision to publish. HS had full access to all data in the study and final responsibility for the decision to submit for publication.

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Author contributions

Hope Simpson - Design of literature search strategy, data extraction form, evidence consensus framework, study selection, data extraction, data analysis, map production, drafted manuscript
Kebede Deribe - Design of evidence consensus framework, revised manuscript for important intellectual content
Earnest Njih Tabah - Provided access to Buruli ulcer surveillance data owned by Cameroon Ministry of Health, revised manuscript for important intellectual content
Adebayo Peters - Provided access to Buruli ulcer surveillance data owned by Nigeria Ministry of Health, revised manuscript for important intellectual content
Issaka Maman - Provided access to Buruli ulcer surveillance data owned by Togo Ministry of Health, revised manuscript for important intellectual content
Michael Frimpong - Assembled Buruli ulcer laboratory dataset at the Kumasi Centre for Collaborative Research in Tropical Medicine, revised manuscript for important intellectual content
Edwin Ampadu - Provided access to Buruli ulcer surveillance data owned by Ghana Ministry of Health, revised manuscript for important intellectual content
Richard Phillips - Provided access to Buruli ulcer laboratory data owned by his own group at the Kumasi Centre for Collaborative Research in Tropical Medicine, revised manuscript for important

intellectual content

Paul Saunderson - Design of the clinical aspect of the evidence consensus framework, revised manuscript for important intellectual content

Rachel L Pullan- Design of evidence consensus framework, revised manuscript for important intellectual content

Jorge Cano - Design of literature search strategy, data extraction form, evidence consensus framework, revised manuscript for important intellectual content

References

1. World Health Organisation. Buruli Ulcer- Number of new reported cases Global Health Observatory Data Repository 2018 [Available from: http://apps.who.int/gho/data/node.main.A1631].
2. Berger S. Tropical Skin Ulcers: Global Status. Gideon Informatics Inc., 2018.
3. World Health Organisation. Buruli ulcer (Mycobacterium ulcerans infection) 2017 [Available from: http://www.who.int/mediacentre/factsheets/fs199/en/].
4. Roltgen K, Pluschke G. Epidemiology and disease burden of Buruli ulcer: a review. *Res Rep Trop Med*. 2015;**6**:59-73
5. Kanga JM. Aspects épidémiologiques de l'ulcère de Buruli en Côte d'Ivoire : résultats d'une enquête nationale. *Bull Soc Pathol Exot*. 2001;**94**:46-51
6. Amofah G, Bonsu F, Tetteh C, et al. Buruli ulcer in Ghana: results of a national case search. *Emerging infectious diseases*. 2002;**8**(2):167-70
7. Noeske J, Kuaban C, Rondini S, et al. Buruli ulcer disease in Cameroon rediscovered. *The American journal of tropical medicine and hygiene*. 2004;**70**(5):520-6
8. Porten K, Sailor K, Comte E, et al. Prevalence of Buruli ulcer in Akonolinga health district, Cameroon: results of a cross sectional survey. *PLoS neglected tropical diseases*. 2009;**3**(6):e466
9. Bretzel G, Siegmund V, Nitschke J, et al. A stepwise approach to the laboratory diagnosis of Buruli ulcer disease. *Trop Med Int Health*. 2007;**12**(1):89-96
10. dos Santos JL. Mycobacterium ulcerans infection in Brazil. *MJA*. 2007
11. Brady OJ, Gething PW, Bhatt S, et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. *PLoS neglected tropical diseases*. 2012;**6**(8):e1760
12. Pigott DM, Bhatt S, Golding N, et al. Global distribution maps of the leishmaniases. *eLife*. 2014;**3**
13. Global Infectious Diseases and Epidemiology Network (GIDEON): a world wide Web-based program for diagnosis and informatics in infectious diseases [Internet]. 2005. Available from: https://www.ebsco.com/products/research-databases/gideon.
14. Cano J, Rebollo MP, Golding N, et al. The global distribution and transmission limits of lymphatic filariasis: past and present. *Parasites & vectors*. 2014;**7**(1):466
15. Global Administrative Areas. GADM database of Global Administrative Areas, version 2.0 2012 [Available from: http://www.gadm.org].
16. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottowa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis [cited 2015 24th November]. Compiled.
17. Deribe K, Cano J, Trueba ML, et al. Global epidemiology of podoconiosis: A systematic review. *PLoS neglected tropical diseases*. 2018;**12**(3):e0006324
18. Association of Public Health Observatories (APHO). Commonly used public health statistics and their confidence intervals. Compiled 2010.
19. World Health Organisation. Recognizing Neglected Tropical Diseases through Changes on The Skin. Compiled 2018.
20. World Health Organisation. Global Health Expenditure Database. Compiled.
21. Evans DB, Tandon A, Murray CJ, et al. Comparative efficiency of national health systems: cross national econometric analysis. *BMJ (Clinical research ed)*. 2001;**323**(7308):307-10
22. Pigott DM, Bhatt S, Golding N, et al. Data from: Global distribution maps of the Leishmaniases. Compiled: Dryad Data Repository; 2014.
23. World Health Organisation. Leprosy data reported to WHO in 2017- provided upon request. 2018
24. Zouré HG, Noma M, Tekle AH, et al. The geographic distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control:(2) pre-control endemicity levels and estimated number infected. *Parasites & vectors*. 2014;**7**(1):326
25. Mitjà O, Marks M, Konan DJ, et al. Global epidemiology of yaws: a systematic review. *The Lancet Global Health*. 2015;**3**(6):e324-e31

26. Coldiron M, Obvala D, Mouniaman-Nara I, et al. The prevalence of yaws among the Aka in the Congo. *Medecine et sante tropicales*. 2013;**23**(2):231-2
27. Remadi L, Haouas N, Chaara D, et al. Clinical presentation of cutaneous leishmaniasis caused by Leishmania major. *Dermatology*. 2016;**232**(6):752-9
28. Mwingira UJ, Downs P, Uisso C, et al. Applying a mobile survey tool for assessing lymphatic filariasis morbidity in Mtwara Municipal Council of Tanzania. *mHealth*. 2017;**3**
29. Saunderson P. Personal communication. Compiled 2018.
30. Johnson R, Sopoh G, Boko M, et al. Distribution de l'infection à Mycobacterium ulcerans (Ulcère de Buruli) dans la commune de Lalo au Bénin. *Trop Med Int Health*. 2005;**10**(9):863-71
31. Sopoh G, Victoire A, Johnson RC, et al. Distribution of Buruli ulcer in the Zè district of Benin. *Médecine tropicale*. 2010 b;**- 70**(- 4):- 383
32. Ecra E, Kanga JM, Gbery ID, et al. - Detection and treatment of early forms of Mycobacterium ulcerans infection in Ivory Coast. 2005;**- 65**(- 4):- 338
33. Mavinga Phanzu D, Suykerbuyk P, Saunderson P, et al. Burden of Mycobacterium ulcerans disease (Buruli ulcer) and the underreporting ratio in the territory of Songololo, Democratic Republic of Congo. *PLoS neglected tropical diseases*. 2013;**7**(12):e2563
34. Amofah GK, Sagoe-Moses C, Adjei-Acquah C, et al. Epidemiology of Buruli ulcer in Amansie West district, Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1993;**87**(6):644-5
35. Ampah KA, Asare P, Binnah DD, et al. Burden and Historical Trend of Buruli Ulcer Prevalence in Selected Communities along the Offin River of Ghana. *PLoS neglected tropical diseases*. 2016;**10**(4):e0004603
36. Behrouznasab K, Razavi MR, Seirafi H, et al. Detection of mycobacterial skin infections by polymerase chain reaction (PCR) amplification of deoxyribonucleic acid (DNA) isolated from paraffin-embeded tissue. *Afr J Microbiol Res*. 2012;**6**(2):279-83
37. Stanford JL. Immunodiffusion Analysis of Strains of Mycobacterium-Ulcerans Isolated in Australia, Malaya, Mexico, Uganda and Zaire. *Journal of Medical Microbiology*. 1973;**6**(3):405-8
38. Global Health Observatory. Buruli ulcer: Situation and trends World Health Organisation [Available from: http://www.who.int/gho/neglected_diseases/buruli_ulcer/en/].
39. Roltgen K, Qi W, Ruf MT, et al. Single nucleotide polymorphism typing of Mycobacterium ulcerans reveals focal transmission of buruli ulcer in a highly endemic region of Ghana. *PLoS neglected tropical diseases*. 2010;**4**(7):e751
40. Eddyani M, Lavender C, de Rijk WB, et al. Multicenter external quality assessment program for PCR detection of Mycobacterium ulcerans in clinical and environmental specimens. *PloS one*. 2014;**9**(2):e89407
41. Johnson RC, Sopoh GE, Boko M, et al. [Distribution of Mycobacterium ulcerans (Buruli ulcer) in the district of Lalo in Benin]. *Tropical medicine & international health : TM & IH*. 2005;**10**(9):863-71
42. Bratschi MW, Bolz M, Minyem JC, et al. Geographic distribution, age pattern and sites of lesions in a cohort of Buruli ulcer patients from the Mape Basin of Cameroon. *PLoS neglected tropical diseases*. 2013;**7**(6):e2252
43. Kanga JM. Epidemiology of Buruli ulcer in Cote d'Ivoire: results of a national survey. *Bulletin De La Societe De Pathologie Exotique*. 2001;**94**(1):46-51

Figure titles and legends

Figure 1: Evidence consensus framework used to assess strength of evidence for BU presence and absence at national level

Part A used for all countries, part B additionally for countries with no evidence of reported cases. Numbers in bold show each constituent's maximum score.
*Score was adjusted *post-hoc* for countries from which *M. ulcerans* strains had been isolated, if no cases meeting inclusion criteria were identified.
PCR = polymerase chain reaction. ZN = Ziehl Neelsen staining.

Figure 2: Evidence consensus framework used to assess strength of evidence for BU presence at sub-national level

Numbers in bold show each constituent's maximum score.

Figure 3: Selection of eligible studies

Figure 4: Evidence consensus for BU presence and absence worldwide

Figure 5: Evidence for Buruli Ulcer Endemicity at National and Upper Sub-National Levels in in Africa

Figure 6: Evidence for Buruli Ulcer Endemicity at National and Upper Sub-National Levels in Central and South America and the Pacific Region.

Figure 7: Evidence for Environmental Occurrence of Mycobacterium ulcerans at Upper Sub-National Level and for Buruli ulcer endemicity at national level in West and Central Africa, the Western Pacific Region, and South America

Table 1: Characteristics of population-based BU prevalence surveys included in the systematic review

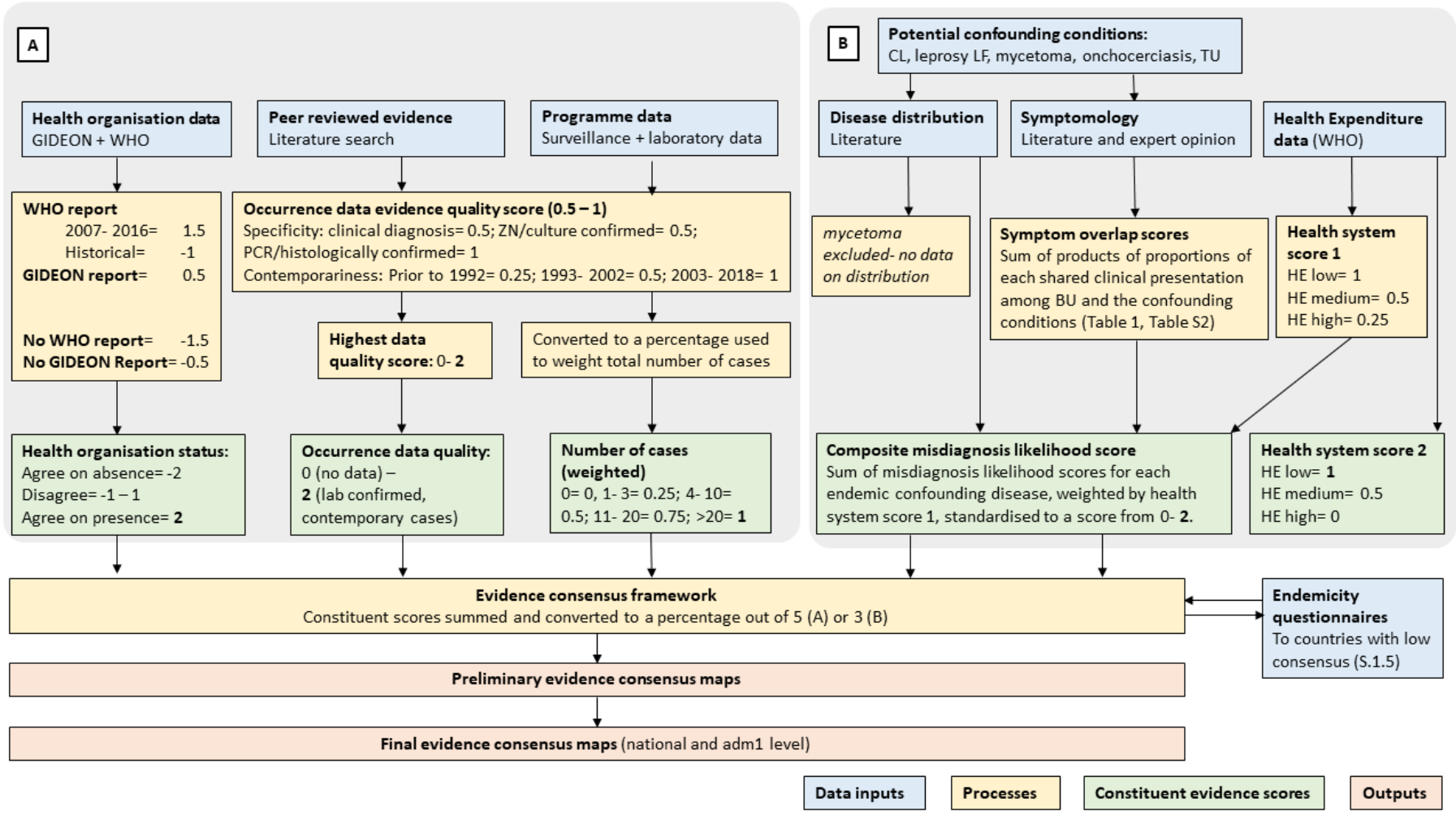
Main author, year published	Country	Year of survey	Location	Study design	Case ascertainment	N. active cases	Sample size	Prevalence (95% CI)		Quality score
Johnson et al., 2005[41]	Benin	2004	Lalo commune	Exhaustive preparatory phase followed by validation of suspected cases	Clinical diagnosis following WHO guidelines	160	86,819	18.4	(15.7- 21.5)	4
Sopoh et al., 2010[31]	Benin	2006	Zè district	Exhaustive preparatory phase followed by validation of suspected cases	Clinical diagnosis following WHO guidelines	222	82,450	26.9	(23.5- 30.7)	4
Noeske et al., 2004[7]	Cameroon	2001	Ayos and Akonolinga health districts	Exhaustive survey in convenience sample of communities with suspect cases	Clinical diagnosis, a subset confirmed by PCR and/or ZN staining	202	98,500	20.5	(17.8- 23.5)	2
Porten et al., 2009[8]	Cameroon	2007	Akonolinga district	Exhaustive survey in a random selection of communities	Clinical diagnosis following WHO guidelines, active and total cases reported separately	56	26,679	21.0	(15.9- 27.3)	5
Bratschi, 2013[42]	Cameroon	2010	Bankim Health District	Exhaustive survey of health district	Clinical diagnosis, a subset confirmed by PCR	25	48,962	5.1	(3.3- 7.5)	3
Kanga 2001[43]	Côte d'Ivoire	1995	Cote d'Ivoire	Exhaustive survey of entire country	Suspect cases identified by CHWs, confirmed by clinicians	4,642	14,500,000	3.2	(3.1- 3.3)	2
Ecra et al., 2005[32]	Côte d'Ivoire	1998	Zoukoougbeu sub-prefecture	Exhaustive survey of entire sub-prefecture	Nodules detected clinically, M. ulcerans confirmed by histopathological analysis	54	47,742	11.3	(8.5- 14.8)	3
Mavinga Phanzu et al., 2013 [33]	DRC	2008	Kimpese and Nsona-Mpangu Rural Health Zones	Exhaustive preparatory phase followed by validation of suspected cases	Clinical diagnosis following WHO guidelines, a subset confirmed by PCR	259	237,418	10.9	(9.6- 12.3)	6
Amofah et al., 1993[34]	Ghana	1991	Amansie West district	Exhaustive survey of entire district	Clinical diagnosis, a subset confirmed by ZN staining	90	130,000	6.9	(5.6- 8.5)	4
Ampah et al., 2016[35]	Ghana	2013	Offin river valley	Exhaustive survey in random sample (n=10) and convenience sample (n=3) of communities within 5km of the Offin River	Clinical diagnosis in following WHO guidelines, a subset confirmed by PCR	7	20,390	3.4	(1.4- 7.1)	6

PCR = polymerase chain reaction. ZN = Ziehl Neelsen staining. DRC = Democratic Republic of Congo. [1]Prevalence of nodules only- did not include other forms of BU

Table 2: Symptom overlap scores (0- 100) for diseases whose symptoms can also be caused by BU.

Confounding disease	Summed score
Tropical Ulcer	70.9
Cutaneous leishmaniasis	35.0
Yaws	16.3
Onchocerciasis	5.7
Leprosy	3.6
Lymphatic filariasis	0.5

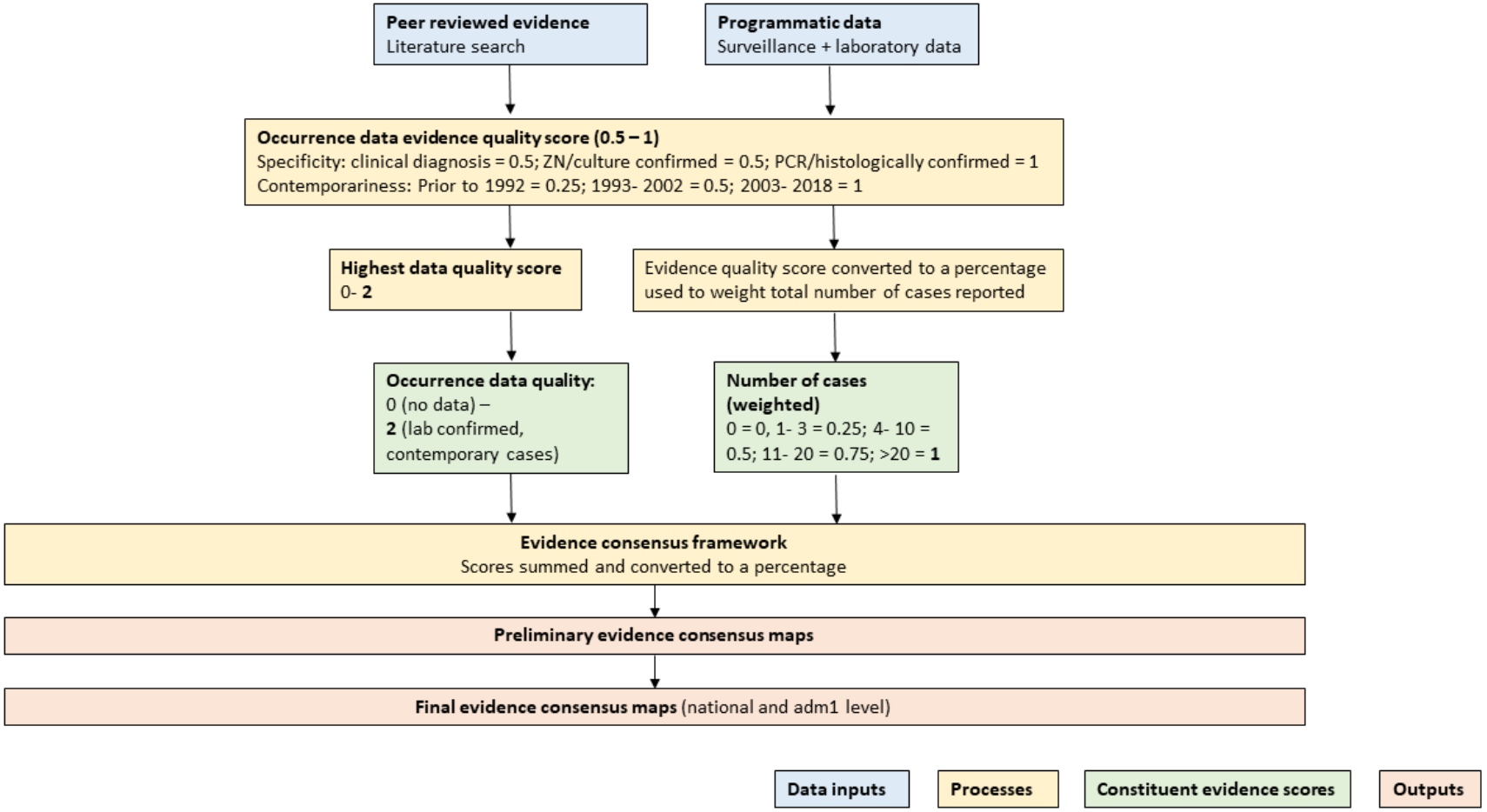
Figure 1: Evidence consensus framework used to assess strength of evidence for BU presence and absence at national level



Part A used for all countries, part B additionally for countries with no evidence of reported cases. Numbers in bold show each constituent's maximum score**.**

ZN = Ziehl Neelsen,

Figure 2: Evidence consensus framework used to assess strength of evidence for BU presence at sub-national level



Numbers in bold show each constituent's maximum score.

Figure 3 Selection of eligible studies

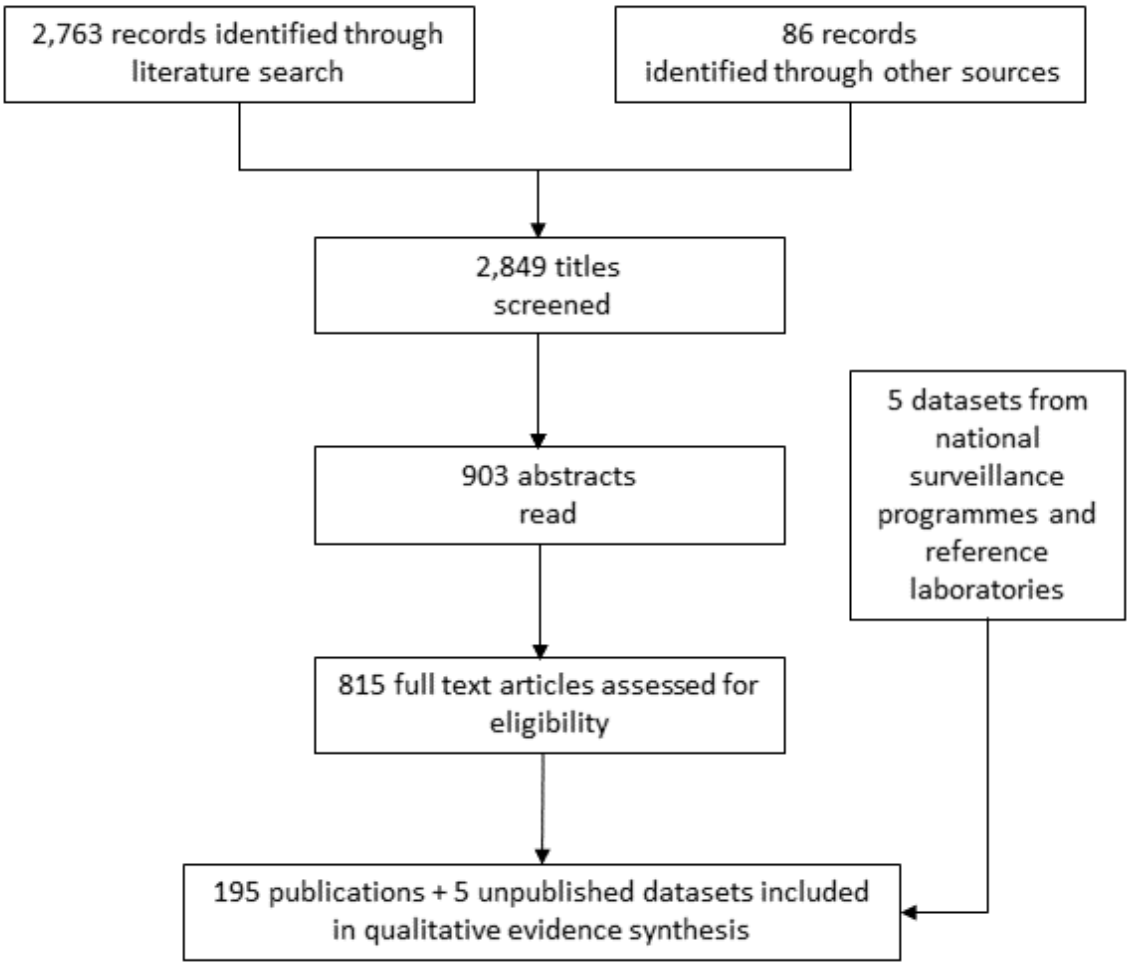


Figure 4: Evidence consensus for BU presence and absence worldwide

Figure 5. Evidence for Buruli Ulcer Endemicity at Upper Sub-National Level in Africa

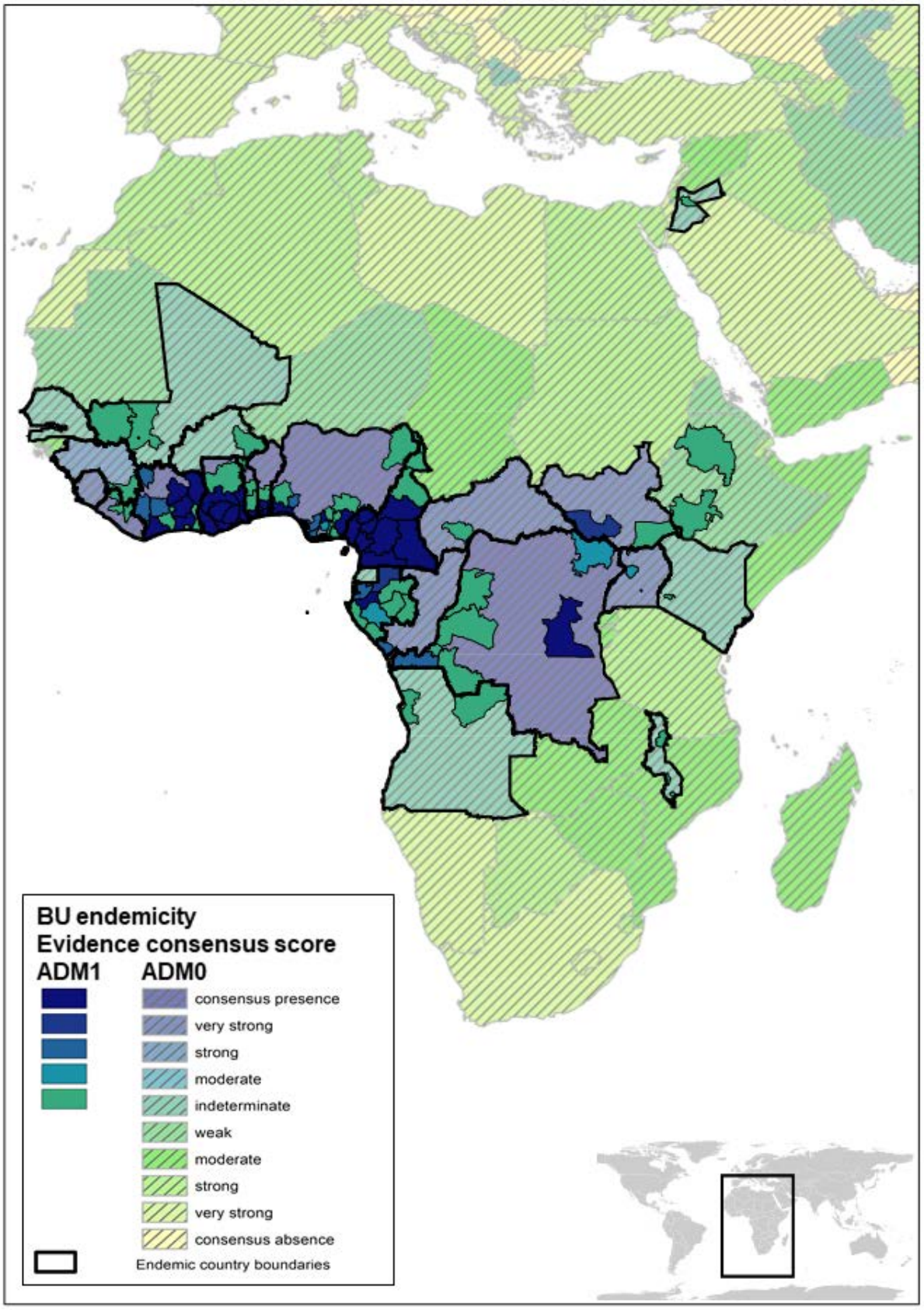


Figure 6. Evidence for Buruli Ulcer Endemicity at National and Upper Sub-National Levels in Central and South America and the Pacific Region.

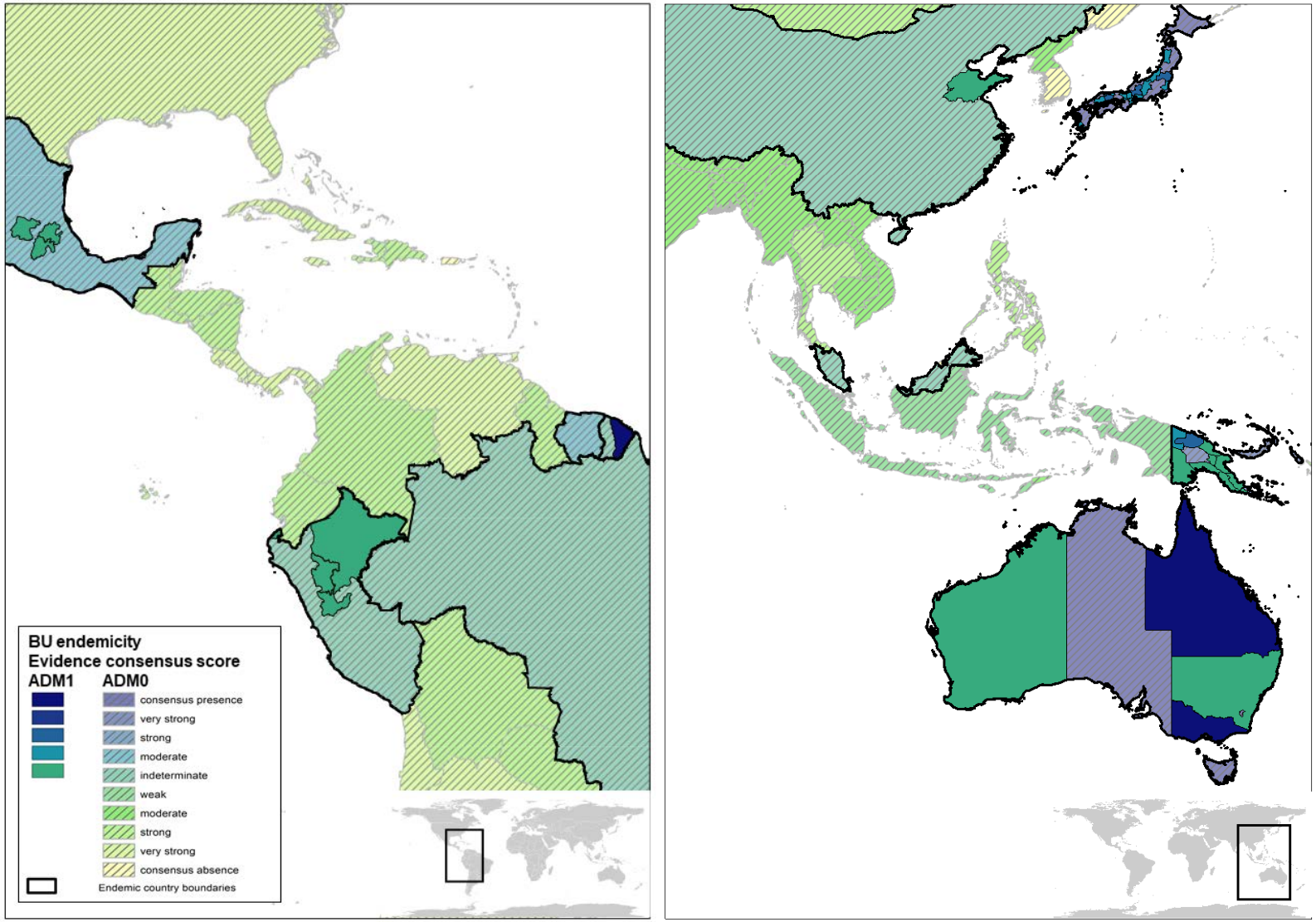


Figure 7. Evidence for Environmental suitability for *Mycobacterium ulcerans* at Upper Sub-National Level and for Buruli ulcer endemicity at upper sub-national level in West and Central Africa, the Western Pacific Region, and the Americas